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Nanomedicine in the treatment of glioblastoma

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Abstract

The current standard of care in glioblastoma management is surgery followed by chemotherapy and radiotherapy. Temozolomide is an alkylating agent most commonly used with a few other second line options. The efficacy of systemic chemotherapy in brain malignancies is limited due to the nature of the blood-brain barrier. Nanomedicine offers one avenue of improving drug delivery to these tumours in a more focussed and effective way in higher doses than currently possible, while simultaneously reducing systemic toxicity.

Keywords: Glioblastoma multiforme, brain tumour, nanotechnology

Introduction

Glioblastoma (GBM), is a WHO grade IV pathology and has a dismal prognosis.[1] Despite advances in treatment, the current therapy based primarily on surgical resection with adjuvant chemotherapy and radiotherapy offers modest temporary disease control.[2] The blood-brain barrier (BBB) is a formidable impediment to drug delivery in the brain which limits the promise of effective chemotherapy in vivo. Nanomedicine offers a unique promise of more precise drug delivery with several options currently under investigation.

Review of literature

Nanoparticles (NPs) are natural, incidental or manufactured materials composed of particles ranging between 1 nm and 100 nm in size. NPs are being investigated as an alternative approach in anticancer therapies in order to improve targeted drug delivery, reduce side effects and avoid drug toxicity and resistance.[3] The strategy can actively transport small molecular drugs, gene medicines and therapeutic proteins to specific tumours including the commonest primary malignant brain tumour, glioblastoma multiforme (GBM). In order to achieve therapeutic targets, drug delivery systems should exhibit high drug loading capacity, good biocompatibility and biodegradability profiles, effective tumour penetration, enhanced cellular internalization, controlled drug release and the ability to evade mononuclear phagocytic system so as to avoid premature degradation of drugs.[4]

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Treatment of malignant brain tumours, particularly GBM is a significant challenge. (Figure). Current GBM therapy is a combination of surgery, radiotherapy and chemotherapy, occasionally coupled with anti-VEGF (Bevacizumab) therapy but since these have been unable to achieve disease control beyond 14-18 months, a constant search for new treatments with improved efficiency and less adverse effects is underway.[5] In an effort to bypass the BBB, high tumour heterogeneity, genetic mutations, active efflux transporters and GBM induced immunosuppression, targeted nanotherapeutics have shown potential to improve pharmacokinetic profile and therapeutic efficacy of drugs as they can be designed to have many favourable characteristics which aid preferential delivery of therapeutic molecules directly to the tumour.[6-9] There is data to support the notion that the efficacy of nanoparticles in GBM is governed by physical and chemical properties of nanomaterials, including their size, shape, surface area, chemistry, charge, functional groups and concentrations as well as nano-biointeractions. In general, smaller sized (<50nm) anionic particles are a more viable option for successful delivery to GBM especially in early disease stages due to their inverse relation to BBB permeability.[6] Shape is important for internalization, cell viability and to attain a longer half-life. The most common shape is spherical, although other shapes such as rods, may be advantageous to avoid immune clearance. NPs for GBM are usually administered intravenously but the intranasal route may be considered as an alternative as it is less invasive and more rapid in action. Other routes such as intra-cranial or intra-tumoural may carry a higher risk of infection and toxicity to healthy neurons.[6] Surface modification compounds such as polyethylene glycol (PEG) derivatives are commonly used to improve NPs stability and reduce opsonization and interaction with protein corona of blood.[9] This is crucial to attain a half-life long enough for the NPs to reach the target site. Several agents other than PEG, however, are being analyzed because of the development of anti-PEG antibodies.[10]

Accumulation of NPs at tumour site in brain depends upon two factors, a passive deposition due to enhanced angiogenesis, leaky vasculature and restricted lymphatic drainage as compared to normal tissue (Enhanced Permeability and Retention or EPR) and active targeting of moieties that are ligands for BBB or glioma receptors

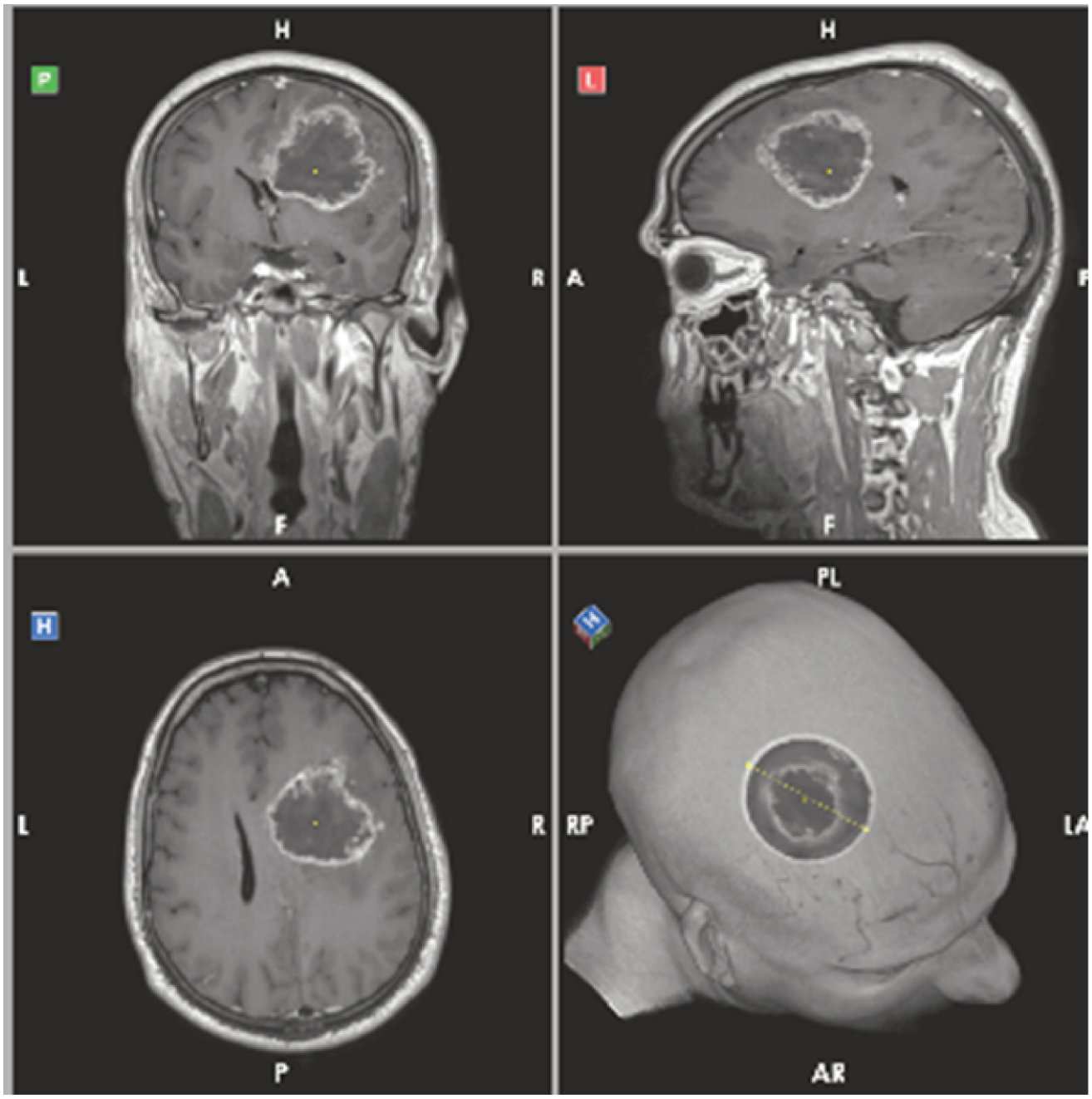

Figure: MRI Brain with contrast (T1 weighted post gadolinium) images demonstrating a left frontal deep glioblastoma. Lesions like these are not suitable for gross total resection due to their relationship with important eloquent areas. NPs delivering effective chemotherapy to such lesions would break new grounds in management.

(lactoferrin and folate) since transport of molecules across BBB is receptor mediated. Furthermore, data is present to suggest promising potential in hitchhiking of NPs on blood cells, preferably monocyte and macrophages, thereby exploiting their abilities to circumvent biological membranes.[6]

Current advances in NPs have generated a wide range of both organic and inorganic NPs that are under investigation for GBM treatment. These include liposomes, polymeric NPs (PNP), lipid nanocarriers (LNC), metal organic framework (MOF), porous silicon (pSi), EnGenIC delivery vehicle(EDV™) and mesoporous silica NPs (MPN) to name a few. Each of these possess, and often share, characteristics that grant certain merits and demerits. Most possess the advantage of penetrating BBB, high drug

loading capacity, biocompatibility and the ability to convey both hydrophilic and hydrophobic drugs.[6,10] In particular, liposome drug delivery systems, EDV™ and pSi are simple and suitable for large scale production.[6,10] Liposomes and PNPs exhibit preferential accumulation of drugs in tumour tissue.[10] MOFs have adjustable structure and the potential to act as adjuvant for radio-sensitization. Psi can not only deliver multiple cargos, but also potentially limit GBM invasiveness. High adsorptive properties and organized pore framework of MSN address the issues with NP stability. Moreover, their modifiable particle size, easily functionable surfaces and ability to improve drug pharmacokinetics and stability profile, shows promise to mitigate challenges involved in drug delivery to the brain.[6] PNPs improve plasma circulation and half-life of drugs, hence, increase bioavailability. LNCs require less raw material, are stable and have a more sustained drug release.[10]

Most of these approaches are under pre-clinical or early clinical trials for both in-vitro and in-vivo models. There are still significant barriers that limit the utilization of NP based drug delivery systems in treatment of GBM. Most significant among these is the safety profile. Further concerns are stability, regulatory mechanisms, variance of pharmacodynamics among different individuals and need for development of techniques to monitor drug accumulation at target site.[2,10] In view of constant experiments, it is believed that in-depth knowledge of mechanisms involved in diffusion kinetics of nanoparticles along with cellular and molecular studies focused on understanding GBM microenvironment, will provide crucial information in the quest to design novel GBM specific nanotherapeutics.[10]

Conclusion

Despite significant challenges, nanoparticle based drug delivery systems are emerging as a promising field for the treatment of glioblastomas. With numerous formulations being tested, the choice of nanomaterial is an ongoing debate which warrants extensive investigation with regard to their biological and toxicological behaviour. Success might still be a long way, but the application of NPs display optimism to increase long term survival rates and possibly revolutionise the treatment of GBM.

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